1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 2, Open-Label, Randomized Study Evaluating the Efficacy and Safety of 3 Doses of Pirtobrutinib in Participants with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Who Previously Received Treatment with a Covalent Bruton Tyrosine Kinase Inhibitor

Brief Title:

A Study Evaluating the Efficacy and Safety of Pirtobrutinib in Participants with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Who Previously Received Treatment with a Covalent Bruton Tyrosine Kinase Inhibitor

Regulatory Agency Identifier Numbers:

IND: 139876

EU trial number: 2024-515689-15-00

Rationale:

This study is an FDA post-marketing requirement (PMR 4557-2) to further assess the efficacy and safety of 3 dose levels of pirtobrutinib in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), who have received 1-3 lines of treatment, including a covalent Bruton tyrosine kinase (BTK) inhibitor.

Although several dose levels were evaluated in the LOXO-BTK-18001 study, relatively few participants were treated at doses lower than 200 mg; thus the need to further explore if a reduced dose could improve the safety profile without compromising efficacy.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To compare the overall response rate of • pirtobrutinib 200 mg to 120 mg, and • pirtobrutinib 200 mg to 60 mg	Overall response rate, as assessed by the investigator per iwCLL 2018. Overall response rate is defined as the proportion of participants who achieve the best overall response at or before the initiation of subsequent anticancer therapy of • CR • CRi • nPR, or

	• PR
Secondary	
To determine the incidence of ≥Grade 3 AESIs that occur at each pirtobrutinib dose level	≥Grade 3 AESIs
To determine the duration of response of each pirtobrutinib dose level	Duration of response. Duration of response is defined as the time from the date of the first documented CR, CRi, nPR, or PR to disease progression (per iwCLL 2018) or death from any cause
To determine the safety and tolerability of each pirtobrutinib dose level	Including, but not limited to • ≥Grade 3 TEAEs • SAEs • discontinuations due to an AE • dose interruptions due to an AE, and • dose reductions due to an AE

Abbreviations: AE = adverse event; AESI = adverse events of special interest; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; nPR = nodular partial remission; PR = partial remission; SAE = serious adverse events; TEAE = treatment-emergent adverse events.

Overall Design:

This is a Phase 2, open-label, randomized study evaluating the efficacy and safety of different dose levels of pirtobrutinib in participants with relapsed or refractory CLL/SLL, who have received 1-3 lines of treatment, including a covalent BTK inhibitor.

This study will further evaluate the safety, tolerability, and efficacy of 3 different dosages of pirtobrutinib, 200 mg, 120 mg, and 60 mg, once daily.

Brief Summary:

The start of treatment at Cycle 1 Day 1 (C1D1) should occur within 5 business days after randomization. With sponsor permission, a maximum of 7 additional days delay between randomization and C1D1 may occur due to holiday, weekend, bad weather, or other unforeseen circumstances.

Participants will receive pirtobrutinib continuously in this study until discontinuation criteria are met or criteria are met for the end of study.

Posttreatment follow-up

Short-term follow-up begins when the participant and investigator agree that the participant will no longer continue study intervention.

Long-term follow-up begins when the participant completes the short-term follow-up visit and ends with either the end of study, withdrawal of consent, loss to follow-up, or the participant's death, whichever is earlier.

Study Population:

In general, an individual may take part in this study if they

- are 18 years of age or older, or are of a legal age in the location in which the study is taking place
- have a confirmed diagnosis of CLL/SLL
- are required to receive treatment for CLL/SLL
- have received at least 1, but not more than 3 lines of, treatment for CLL/SLL and have received a covalent BTK inhibitor as one of those treatments, and
- are able to walk around on their own and take care of themselves.

In general, an individual may not take part in this study if they

- have had another type of cancer in the past 3 years. Exceptions may occur with documented sponsor approval. Examples of exceptions include
  - skin cancer that is not a melanoma
  - abnormal cells in the cervix that have not spread to other parts of the body
  - prostate cancer that was completely inside the prostate gland and did not spread, and
  - breast cancer that did not spread beyond the breast tissue and has not been present for more than 3 years.
- have major surgery planned in the near future
- have a history of significant cardiovascular disease, and
- have certain diseases of the liver or an injured liver due to previous drug treatments.

Number of Participants:

Approximately 249 participants will be randomly assigned in a 1:1:1 ratio to study intervention.

Intervention Groups and Duration:

This study will evaluate 3 dose levels of pirtobrutinib, 200 mg, 120 mg, and 60 mg, once daily. Participants will receive pirtobrutinib continuously in this study until discontinuation criteria are met or criteria are met for the end of study.

Ethical Considerations of Benefit/Risk:

The safety and effectiveness of pirtobrutinib treatment for participants with CLL/SLL support the overall benefit-risk of individuals taking part in this study.

Data Monitoring Committee: No

An assessment committee internal to Lilly will review safety and efficacy data during the study.